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• REVIEW •

Drug therapy for ulcerative colitis

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Abstract

Ulcerative colitis (UC) is an inflammatory destructive disease of the large intestine occurred usually in the rectum and lower part of the colon as well as the entire colon. Drug therapy is not the only choice for UC treatment and medical management should be as a comprehensive whole. Azulfidine, Asacol, Pentasa, Dipentum, and Rowasa all contain 5-aminosalicylic acid (5-ASA), which is the topical anti-inflammatory ingredient. Pentasa is more commonly used in treating Crohn's ileitis because Pentasa capsules release more 5-ASA into the small intestine than Asacol tablets. Pentasa can also be used for treating mild to moderate UC. Rowasa enemas are safe and effective in treating ulcerative proctitis and proctosigmoiditis. The sulfa-free 5-ASA agents (Asacol, Pentasa, Dipentum and Rowasa) have fewer side effects than sulfa-containing Azulfidine. In UC patients with moderate to severe disease and in patients who failed to respond to 5-ASA compounds, systemic (oral) corticosteroids should be used. Systemic corticosteroids (prednisone, prednisolone, cortisone, *etc.*) are potent and fast-acting drugs for treating UC, Crohn's ileitis and ileocolitis. Systemic corticosteroids are not effective in maintaining remission in patients with UC. Serious side effects can result from prolonged corticosteroid treatment. To minimize side effects, corticosteroids should be gradually reduced as soon as the disease remission is achieved. In patients with corticosteroid-dependent or unresponsive to corticosteroid treatment, surgery or immunomodulator is considered. Immunomodulators used for treating severe UC include azathioprine/6-MP, methotrexate, and cyclosporine. Integrated traditional Chinese and Western medicine is safe and effective in maintaining remission in patients with UC.

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory destructive disease of the large intestine characterized by motility and secretion disorders. Inflammation usually occurs in the rectum and lower part of the colon, but it may affect the entire colon[1-4]. UC rarely affects the small intestine except for the end section, called the terminal ileum. UC may also be called colitis or proctitis[4, 5].

Inflammation makes the colon empty frequently, causing diarrhea. Ulcers formed in places where the inflammation has killed the cells of colon, bleeding ulcers and pus discharge. UC is an inflammatory bowel disease (IBD) that causes inflammation in the small intestine and colon. UC can be difficult to diagnose because its symptoms are similar to other intestinal disorders and another type of IBD called Crohn's disease (CD). CD differs from UC because it causes deeper inflammation within the intestinal wall[5-7]. Also, CD usually occurs in the small intestine, although it can also occur in the mouth, esophagus, stomach, duodenum, large intestine, appendix, and anus. UC may occur in people of any age, but most often it starts between ages 15 and 30, or less frequently between ages 50 and 70. Children and adolescents sometimes develop the disease. UC affects men and women equally and appears to run in some families.

UC CHARACTERISTICS

Of the estimated two million Americans suffer from IBD, CD is far less common than UC, but currently the incidences of each are estimated to be about equal. The incidence may vary depending on gender, age, and geography[4-6]. Men and women have an equal risk for UC. IBD is diagnosed most often in young people between the ages of 10 and 19, but it can occur at any age. A smaller peak onset occurs between 50 and 80 years. About 2% of IBD cases appear in children below age 10. UC is most common among people of European descent. People of African descent have a lower incidence than Caucasians. Low incidence regions include Asia and South America. Ethnically, Jewish people have a higher risk. UC may disproportionately affect people of higher socioeconomic classes, but evidence for this is inconclusive.

UC shares certain characteristics[4-8]: (1) Symptoms usually appear in young adults. (2) Symptoms can develop gradually or suddenly. (3) Both are chronic. The symptoms may flare up (relapse) after symptom-free periods (remission) or symptoms may be continuous without treatment. (4) The disease can be mild or very severe and disabling. (5) The severity of symptoms and relapse rates of both UC and DC vary with seasons, with the highest risk in winter and autumn and lowest in summer.

Factors associated with UC

Smokers have lower than average rates of UC (but higher than average rates of CD). In fact, it has been reported that some patients with UC had disorders after they gave up smoking, and many studies have stressed the association between smoking and protection against UC. This information is certainly no encouragement to smoke. Rather, patients should ask their physician about trials using nicotine replacement aids. Breast feeding also appears to be associated with lower risk of UC. Left-handed people have a significantly higher risk for both IBDs and other diseases associated with immune abnormalities. A 2001 study reported that patients with UC were more likely to have a history of depression or anxiety than those without IBD. Some researchers suggested that depression might alter the immune system and make people more susceptible to UC[3,4].

Symptoms of UC

General symptoms Fever may occur with severe attacks, usually a low-grade. Spiking fever and chills indicate complications. Loss of appetite, weight loss and impaired growth in children are usually not evidence of mild or moderate or severe UC. Increased frequency, a feeling of incomplete evacuation, tenesmus (a painful urge for a bowel movement even if the rectum is empty) and fecal incontinence may occur in mild or severe stage. Anal ulcers and fistulae, channels that can burrow between organs, loops of intestine or between intestines and skin, may be early symptoms. Recurrent diarrhea is very common, but the onset may be very gradual and mild or silent. Feces may also contain mucus. Recurrent diarrhea is prevalent in developing countries, particularly in tropical regions[6-8]. Blood is always present in stools, it may be readily visible or visible only using a microscope (so-called occult blood). Constipation can be a symptom of UC but not as common as diarrhea. It can occur during flare-ups, and when the inflamed rectum triggers a reflex response in the colon that causes it to retain the stool. But constipation in CD is usually a symptom of obstruction in the small intestine.

Abdominal symptoms Pain is not a prominent symptom but can vary. Vague discomfort may occur in the lower abdomen, an ache around the top of the hipbone, or cramps in the middle of the abdomen. Severe pain can occur during flare-ups. Recurrent episodes of pain in the lower right part of the abdomen or above the pubic bone often precede and are relieved by defecation. Bloating, nausea, and vomiting may also occur. Intestinal pain may also be an indication of serious conditions, such as an abscess, or a perforation of the intestinal wall.

Complications of UC Patients with UC limited to the rectum (proctitis) or colitis limited to the end of the left colon (proctosigmoiditis) usually do quite well. Short periodic treatments using oral medications or enemas may be sufficient. Serious complications are rare in these patients. In those with a more extensive disease, blood loss from the inflamed intestines can lead to anemia, and may require treatment with iron supplements or even blood transfusions. Rarely, the colon can acutely dilate to a large size when the inflammation becomes very severe. This condition is called toxic megacolon. Patients with toxic megacolon are extremely ill with fever, abdominal pain and distention, dehydration, and malnutrition. Unless the patient improves rapidly with medication, surgery is usually necessary to prevent colon rupture[3-5,7,8].

Colon cancer is a recognized complication of chronic UC. The risk for cancer begins to rise significantly after 8 to 10 years of colitis. The risk of a patient with UC developing colon cancer is also related to the location and the extent of the disease. Patients with only ulcerative proctitis probably do not have increased colon cancer risk compared to the general population. Among patients with active pancolitis of 10 years or longer, their risk of colon cancer is 10-20 times higher that of the general population. In patients with chronic left-sided colitis, the risk of colon cancer is increased but not as high as in patients with chronic pancolitis.

Since these cancers have a more favorable outcome when treated at an earlier stage, yearly colon examination is recommended after 8 years of a known extensive disease. During these examinations, samples of tissue (biopsies) should be taken to search for precancerous lesions in the lining cells of the colon. When precancerous lesions are found, removal of the colon may be necessary to prevent colon cancer.

Complications of UC involve other parts of the body. Ten percent of the patients can develop inflammation of the joints (arthritis). Some patients have low back pain due to arthritis of the sacroiliac joints. Rarely, patients may develop painful and red skin nodules (erythema nodosum). Yet others can have painful and red eyes (uveitis, episcleritis). Because these particular complications are a permanent risk in vision impairment, eye pain or redness is symptoms that require a physician's evaluation. Diseases of the liver and bile ducts may associate with UC. For example, in rare patients with a condition called sclerosing cholangitis, repeated infections and inflammation in the bile ducts can lead to recurrent fever, yellowing of skin (jaundice), cirrhosis, and the need for a liver transplant.

DRUG TREATMENT

Both medications and surgery have been used to treat UC[7-21]. However, surgery is reserved for those with severe inflammation and life-threatening complications. There is no medication that can cure UC. Patients with UC will typically experience periods of relapse (worsening of inflammation) followed by periods of remission lasting for mo to years. During relapses, symptoms of abdominal pain, diarrhea, and rectal bleeding can worsen patients' quality of life. During remissions, these symptoms subside. Remissions usually occur because of treatment with medications or surgery, but occasionally they occur spontaneously.

Since UC cannot be cured by medications, the goals of treatment with medications are to induce remissions, maintain remissions, minimize side effects of treatment, and improve the quality of life. The treatment of UC with medications is similar, though not always identical, to the treatment of CD[9-11,16-20].

Medications treating UC include anti-inflammatory agents such as 5-ASA compounds, systemic and topical corticosteroids, and immunomodulators.

Anti-inflammatory medications that decrease intestinal inflammation are analogous to arthritis medications that decrease joint inflammation (arthritis). The anti-inflammatory medications used in the treatment of UC are topical 5-ASA compounds such as sulfasalazine (Azulfidine), olsalazine (Dipentum), and mesalamine (Pentasa, Asacol, Rowasa enema) that need direct contact with the inflamed tissues in order to be effective. Systemic corticosteroids can decrease the inflammation throughout the body without direct contact with the inflamed tissue. Systemic corticosteroids have predictable side effects in long-term treatment. Immunomodulators are medications that suppress the body's immune system either by reducing the cells that are responsible for immunity, or by interfering with proteins that are important in promoting inflammation. Immunomodulators are increasingly becoming important for patients with severe UC who do not respond adequately to anti-inflammatory agents. Examples of immunomodulators include 6-mercaptopurine (6-MP), azathioprine, methotrexate, and cyclosporine.

A somewhat curious new treatment is nicotine. It has long been observed that the risk of UC appears to be higher nonsmokers and in ex-smokers. In certain circumstances, patients could improve clinically when treated with nicotine while they failed to respond to other medications.

5-ASA compounds (azulfidine, asacol, pentasa, dipentum)

5-ASA (5-aminosalicylic acid), also called mesalamine, is chemically similar to aspirin. Aspirin (acetylsalicylic acid) has been used for many years in treating arthritis, bursitis, and tendinitis (conditions of tissue inflammation). Aspirin, however, is not effective in treating UC. On the other hand, 5-ASA is effective in treating UC if the drug can be delivered directly (topically) onto the inflamed colon lining[17-21]. For example, Rowasa for enema is a 5-ASA solution that is effective in treating inflammation in and near the rectum (ulcerative proctitis and ulcerative proctosigmoiditis). However, the enema solution cannot reach high enough to treat inflammation in the upper colon. Therefore, for most patients with UC, 5-ASA must be taken orally. When pure 5-ASA is taken orally, however, the

stomach and upper small intestine absorb most of the drug before it reaches the colon. Therefore, to be effective as an oral agent for UC, 5-ASA has to be modified chemically to escape absorption by the stomach and upper intestines. These modified 5-ASA compounds are sulfasalazine (Azulfidine), mesalamine (Pentasa, Asacol), and olsalazine (Dipentum).

Azulfidine

Sulfasalazine (Azulfidine)[22] has been used successfully for many years in inducing remission among patients with mild to moderate UC. Inducing remission means decreasing intestinal inflammation and relieving symptoms of abdominal pain, diarrhea, and rectal bleeding. Sulfasalazine has also been used for prolonged periods of time to maintain remissions.

Sulfasalazine consists of a 5-ASA molecule linked chemically to a sulfapyridine molecule. (Sulfapyridine is a sulfa antibiotic). Connecting the two molecules together prevents absorption by the stomach and upper intestines prior to reaching the colon. When sulfasalazine reaches the colon, bacteria in the colon will break the linkage between the two molecules. After breaking away from 5-ASA, sulfapyridine is absorbed into the body and then excreted in the urine. Most of the active 5-ASA, however, remains in the colon to treat colitis.

Most of the side effects of sulfasalazine are due to the sulfapyridine molecule. These side effects include nausea, heartburn, headache, anemia, skin rashes, and in rare instances, hepatitis and kidney inflammation. In men, sulfasalazine can reduce the sperm count which sperm count is reversible, and the count usually returns to normal after discontinuing sulfasalazine or by changing to a different 5- ASA compound.

The benefits of sulfasalazine generally are dose related. Therefore, high doses of sulfasalazine may be necessary to induce remission. Some patients cannot tolerate high doses because of nausea and stomach upset. To minimize stomach upset, sulfasalazine is generally taken after or with meals. Some patients find it easier to take Azulfidine-EN (enteric-coated form of sulfasalazine). Enteric-coating helps decrease stomach upset. The newer 5-ASA compounds do not have the sulfapyridine component and have fewer side effects than sulfasalazine.

Asacol

Asacol is a tablet consisting of 5-ASA compound, mesalamine, surrounded by an acrylic resin coating (Asacol is sulfa free)[22,23]. The resin coating prevents 5-ASA from being absorbed as it passes through the stomach and small intestine. When the tablet reaches the terminal ileum and colon, the resin coating dissolves, thus releasing 5-ASA into the colon.

Asacol is effective in inducing remissions in patients with mild to moderate UC. It is also effective when used for prolonged periods of time to maintain remissions. The recommended dose of Asacol to induce remission is two 400-mg tablets three times daily (total of 2.4 g/d). Two tablets of Asacol twice daily (1.6 g/d) are recommended for maintaining remission. Occasionally, the maintenance dose should be higher. As Azulfidine, the benefits of Asacol are dose-related. If patients do not respond to 2.4 g/d of Asacol, the dose is frequently increased to 3.6 g/d (and sometimes even higher) to induce remission. If patients fail to respond to the higher doses of Asacol, then alternatives such as corticosteroids are recommended.

Pentasa

Pentasa is a capsule consisting of 5-ASA compound mesalamine inside controlled-release spheres. Like Asacol, it is sulfa free. As the capsule travels down the intestines, 5-ASA inside the spheres is slowly released into the intestines. Unlike Asacol, mesalamine in Pentasa is released into the small intestine as well as colon. Therefore, Pentasa can be effective in treating inflammation in the small intestine and colon. Pentasa is currently the most logical 5-ASA compound for treating mild to moderate CD involving the small intestine. Pentasa is also used to induce remission and maintain remission among patients with mild to moderate UC[23,24].

Olsalazine (Dipentum)

Olsalazine (Dipentum) consists of two 5-ASA molecules linked together[24,25]. It is sulfa free. The linked 5-ASA molecules travel through the stomach and the small intestine unabsorbed. When the drug reaches the terminal ileum and the colon, normal bacteria in the intestine break the linkage and release the active drug into the colon and terminal ileum. Olsalazine has been used in treating UC and maintaining remissions. A side effect unique to olsalazine is secretory diarrhea (diarrhea resulting from excessive production of fluid in the intestines). This condition occurs in 5-10% of patients, and diarrhea sometimes can be severe.

Colazal

Colazal (balsalazide) is a capsule in which 5-ASA is linked by a chemical bond to another molecule that is inert (without effect on the intestine) and prevents 5-ASA from being absorbed[25-29]. This drug is able to travel through the intestine unchanged until it reaches the end of the small bowel (terminal ileum) and colon. There, intestinal bacteria break apart 5-ASA and the inert molecule, releasing 5-ASA. Because intestinal bacteria are most abundant in the terminal ileum and colon, Colazal is used to treat inflammation predominantly localized to the colon. Colazal recently has been approved by FDA for use in United States of America.

More clinical trials are needed to compare the effectiveness of Colozal to other mesalamine compounds such as Asacol in treating UC. Therefore in United States of Amerrica, 5-ASA, has to be individualized[27,28]. Colozal should be prescribed for patients who cannot tolerate or fail to respond to Asacol, also for patients with predominantly left sided colitis, since some studies seem to indicate that Colozal is effective in treatieng left sided colitis.

Rowasa enema

Rowasa is 5-ASA compound mesalamine in enema form and is effective in the treatment of ulcerative proctitis and ulcerative proctosigmoiditis (two conditions where active 5-ASA drugs taken as enemas can easily reach the inflamed tissues directly)[29,30]. Each Rowasa enema contains 4 g of mesalamine in 60 mL of fluid. The enema is usually administered at bedtime, and patients are encouraged to retain the enema through the night.

The enema contains sulfite and should not be used by patients with sulfite allergy. Otherwise, Rowasa enemas are safe and well tolerated.

Rowasa also comes in suppository form for treating limited proctitis. Each suppository contains 500 mg of mesalamine and usually is administered twice daily. While some patients improve within several days after using Rowasa, the usual course of treatment is 3-6 wk. Some patients may need even longer courses of treatment for optimal benefit. In patients who do not respond to Rowasa, oral 5-ASA compounds (such as Asacol) can be added. Some studies have reported increased effectiveness in treating ulcerative proctitis and proctosigmoiditis by combining oral 5-ASA compounds with Rowasa enemas. Oral 5-ASA compounds are also used to maintain remission in ulcerative proctitis and proctosigmoiditis[30].

Another alternative for patients who fail to respond to Rowasa or who cannot use Rowasa is cortisone enemas (Cortenema). Cortisone is a corticosteroid that is a potent anti-inflammatory agent. Oral corticosteroids are systemic drugs with serious and predictable long-term side effects. Cortenema is a topical corticosteroid that is less absorbed into the body than oral corticosteroids, and therefore, it has fewer and less side effects.

Side effects of 5-ASA compounds

Sulfa-free 5-ASA compounds have fewer side effects than sulfasalazine and also do not impair male fertility. In general, they are safe medications for long-term use and well tolerated[23-28]. Patients allergic to aspirin should avoid 5-ASA compounds because they are chemically similar to aspirin. In a few occasions kidney inflammation has been reported due to the use of 5-ASA compounds. These compounds should be used with caution in patients with known kidney disease. It also is recommended that blood tests of kidney function are obtained before and during the treatment.

A rare instance of acute worsening of diarrhea, cramps, and abdominal pain may occur at times and may be accompanied by fever, rash, and malaise. This reaction is believed to represent an allergy to t5-ASA compounds.

Corticosteroids for UC

Corticosteroids (prednisone, prednisolone, hydrocortisone, *etc*.) have been used for many years in the treatment of patients with moderate to severe CD and UC or who fail to respond to optimal doses of 5-ASA compounds[31-34]. Unlike 5-ASA compounds, corticosteroids do not require direct contact with inflamed intestinal tissues to be effective. Oral corticosteroids are potent anti-inflammatory agents. After absorption, corticosteroids exert prompt anti-inflammatory action throughout the body. Consequently, they are used in treating Crohn's enteritis, ileitis, and ileocolitis, as well as UC and Crohn's colitis. In critically ill patients, intravenous corticosteroids (such as hydrocortisone) can be given in the hospital. Corticosteroids are faster acting than 5-ASA compounds. Patients frequently experience improvement in their symptoms within days after using starting corticosteroids. Corticosteroids, however, do not appear to be useful in maintaining remissions in UC[22-24].

Proper use of corticosteroids

Once the decision is made to use oral corticosteroids, treatment usually is initiated with prednisone, 40-60 mg daily. The majority of patients with UC respond with an improvement in symptoms. Once symptoms improve, prednisone is reduced by 5-10 mg per wk until the dose of 20 mg per day is reached. The dose then is tapered at a slower rate until prednisone ultimately is discontinued. Gradually reducing corticosteroids not only minimizes the symptoms of adrenal insufficiency, but also reduces the chances of abrupt relapse of colitis.

Many doctors use 5-ASA compounds at the same time as corticosteroids. In patients who achieve remission with systemic corticosteroids, 5-ASA compounds such as Asacol are often continued to maintain remissions[10,17-19]. In patients whose symptoms return during reduction of the dose of corticosteroids, the dose of corticosteroids is increased slightly to control the symptoms. Once the symptoms are under control, the reduction can resume at a slower pace. Some patients become corticosteroid dependent and consistently develop symptoms of colitis whenever the corticosteroid dose is below a certain level. In patients who are corticosteroid dependent or unresponsive to corticosteroids, other anti-inflammatory medications, immunomodulator medications or surgery are considered. The management of patients who are corticosteroid dependent or patients with a severe disease which responds poorly to medications is complex. Doctors who are experienced in treating inflammatory bowel disease and in using immunomodulators should evaluate these patients.

Side effects of corticosteroids

Side effects of corticosteroids depend on the dose and duration of treatment. Short courses of prednisone, for example, usually are well tolerated with few and mild side effects. Long term high doses of corticosteroids usually produce predictable and potentially serious side effects. Common side effects include rounding of the face (moon face), acne, increased body hair, diabetes, weight gain, high blood pressure, cataracts, glaucoma, increased susceptibility to infections, muscle weakness, depression, insomnia, mood swings, personality changes, irritability, and thinning of bones (osteoporosis) with an accompanying increased risk of compression fractures of the spine. Children on corticosteroids can experience stunted growth.

The most serious complication of long-term corticosteroid use is aseptic necrosis of the hip joints. Aseptic necrosis means death of bone tissue. It is a painful condition that can ultimately lead to the need for surgical replacement of the hips. Aseptic necrosis also has been reported in knee joints. It is unknown how corticosteroids cause aseptic necrosis. The estimated incidence of aseptic necrosis among corticosteroid users is 3-4%. Patients on corticosteroids who develop pain in hips or knees should report the pain to their doctors promptly. Early diagnosis of aseptic necrosis with cessation of corticosteroids has been reported in some patients to decrease the severity of the disease and possibly help avoid hip replacement.

Prolonged use of corticosteroids can depress the ability of adrenal glands to produce cortisol (a natural corticosteroid necessary for proper functioning of the body). Abruptly discontinuing corticosteroids can cause symptoms due to a lack of natural cortisol (a condition called adrenal insufficiency). Symptoms of adrenal insufficiency include nausea, vomiting, and even shock. Withdrawing corticosteroids too quickly can also produce symptoms of joint aches, fever, and malaise. Therefore, corticosteroids need to be gradually reduced rather than abruptly stopped. Even after corticosteroids are discontinued, the ability of adrenal glands' to produce cortisol can remain depressed for mo to two years. The depressed adrenal glands may not be able to produce enough cortisol to help the body handle stresses such as accidents, surgery, and infections. These patients will need treatment with corticosteroids (prednisone, hydrocortisone, *etc*.) during stressful situations to avoid developing adrenal insufficiency. Because corticosteroids are not useful in maintaining remission in UC and CD and because they have predictable and potentially serious side effects, these drugs should be used for the shortest possible time.

Preventing corticosteroid-induced osteoporosis

Long-term use of corticosteroids such as prednisolone or prednisone can cause osteoporosis, because corticosteroids could decrease calcium absorption from intestines and increase loss of calcium from the kidneys and bones. Increasing dietary calcium intake is important but alone cannot halt corticosteroid-induced bone loss. Management of patients on long-term corticosteroids should include adequate calcium (1 000 mg/d if premenopausal, 1 500 mg/d if postmenopausal) and vitamin D (800 U/d) intake, needs for continued corticosteroid treatment and the lowest effective dose, a bone density study to measure the extent of bone loss in patients taking corticosteroids for more than 3 mo, regular weight-bearing exercise and stopping cigarette smoking, discussion with the doctor regarding the use of alondronate (Fosamax) or risedronate (Actonel) in prevention and treatment of corticosteroid induced osteoporosis.

Immunomodulator medications

Immunomodulators are medications that weaken the body's immune system, which is composed of immune cells and cell-produced proteins. These cells and proteins serve to defend the body against harmful bacteria, viruses, fungi, and other foreign invaders. Activation of the immune system causes

inflammation within the tissues where the activation occurs. Normally, the immune system is activated only when the body is exposed to harmful invaders. In patients with CD and UC, however, the immune system is abnormally and chronically activated in the absence of any known invaders. Immunomodulators decrease tissue inflammation by reducing the population of immune cells and/or by interfering with their production of proteins that promote immune activation and inflammation. Generally, the benefits of controlling moderate to severe UC outweigh the risks of infection due to weakened immunity. Examples of immunomodulators include azathioprine (Imuran), 6-mercaptopurine (6-MP, Purinethol), cyclosporine (Sandimmune), and methotrexate[31-37].

Azathoprine (imuran) and 6-MP (purinethol)

Azathioprine and 6-mercaptopurine (6-MP) are medications that weaken the body's immunity by reducing the population of a class of immune cells called lymphocytes[31]. Azathioprine and 6-MP are related chemically. Specifically, azathioprine is converted into 6-MP inside the body. In high doses, these two drugs are useful in preventing rejection of transplanted organs and in treating leukemia. In low doses, they are used to treat patients with moderate to severe CD and UC. Azathioprine and 6-MP are increasingly recognized by doctors as valuable drugs in treating CD and UC. Some 70% of patients with moderate to severe disease benefit from these drugs. Because of the slow onset of action and the side effects, 6-MP and azathioprine are used mainly in the following situations[31-34], UC and CD patients with severe diseases not responding to corticosteroids, patients experiencing undesirable corticosteroid-related side effects, patients dependent on corticosteroids and unable to discontinue them without developing relapses.

When azathioprine and 6-MP are added to corticosteroids in the treatment of UC patients who do not respond to corticosteroids alone, they may have an improved response to smaller doses, and shorter courses of corticosteroids may be used. Some patients can discontinue corticosteroids without experiencing relapses. The ability to reduce corticosteroid has earned the reputation of 6-MP and azathioprine as "steroid-sparing" medications[32-34]. In severe UC patients with severe disease who suffer frequent relapses, 5-ASA may not be sufficient, and more potent azathioprine and 6-MP will be necessary to maintain remissions. In the doses used for treating UC and CD, the long-term side effects of azathioprine and 6-MP are less serious than long-term oral corticosteroids or repeated courses of oral corticosteroids.

Side effects of 6-MP and azathioprine

Side effects of 6-MP and azathioprine include increased vulnerability to infections, inflammation of the liver (hepatitis) and pancreas (pancreatitis), and bone marrow toxicity (interfering with the formation of cells that circulate in the blood)[31-37].

The goal of treatment with 6-MP and azathioprine is to weaken the body's immune system in order to decrease the intensity of inflammation in intestines. However, weakening the immune system increases the vulnerability to infections. For example, in a group severe CD patients unresponsive to standard doses of azathioprine, raising the dose of azathioprine helped to control the disease, but two patients developed cytomegalovirus (CMV) infection.

Azathioprine and 6-MP-induced inflammation of the liver (hepatitis) and pancreas (pancreatitis) is rare. Pancreatitis typically causes severe abdominal pain and sometimes vomiting. Pancreatitis due to 6-MP or azathioprine occurs in 3-5% of patients, usually during the first several wk of treatment. Patients who develop pancreatitis should not receive either of these two medications again[38,39]. Azathioprine and 6-MP also suppress the bone marrow where red blood cells, white blood cells, and platelets are made. Actually, a slight reduction in white blood cell count during treatment is desirable since it indicates that the dose of 6-MP or azathioprine is high enough to have an effect. However, excessively low red or white blood cell counts indicate bone marrow toxicity. Therefore, patients on 6-MP and azathioprine should have periodic detection of blood counts (usually every two wk initially and then every 3 mo during maintenance) to monitor the effect of the drugs on their bone marrow. 6-MP can reduce the sperm count in men. When the partners of male patients on 6-MP conceive, there is a higher incidence of miscarriages and vaginal bleeding. There also are respiratory difficulties in the newborn. Therefore, it is recommended that whenever feasible, male patients should stop 6-MP and azathioprine for 3 mo before conception. Patients on long-term high dose azathioprine to prevent rejection of the kidney after kidney transplantation have an increased risk of lymphoma. There is no evidence at present that long-term use of azathioprine and 6-MP in low doses used in IBD increases the risk of lymphoma, leukemia or other malignancies[6,40].

6-MP characteristics

One problem with 6-MP and azathioprine is their slow onset of action. Typically, 3 mo or a longer time is required to achieve the full benefit of these drugs. During this time, corticosteroids frequently have to be maintained at high levels to control inflammation[33].

The reason for this slow onset of action is partly due to the way prescribed 6-MP by doctors. Typically, 6-MP is started at a dose of 50 mg/d. The blood count is then checked 2 wk later. If the white blood cell count (specifically the lymphocyte count) is not reduced, the dose is increased. This cautious, stepwise approach helps prevent severe bone marrow and liver toxicity, but delays benefit from the drug.

Studies have shown that giving higher doses of 6-MP early can speed up the benefit of 6-MP without increasing toxicity in most patients, but some patients do develop severe bone marrow toxicity. Therefore, the dose of 6-MP has to be individualized. Scientists now believe that an individual's vulnerability to 6-MP toxicity is genetically inherited. Blood tests can be performed to identify those individuals with increased vulnerability to 6-MP toxicity. In these individuals, lower initial doses can be used. Blood tests can also be performed to measure the levels of certain by-products of 6-MP[32-34]. The levels of these by-products in the blood help doctors more quickly determine whether the dose of 6-MP is right for the patient.

6-MP maintained treatment

Patients on maintainance with 6-MP or azathioprine for years have not any important long-term side effects. Their doctors, however, should closely monitor their patients on long-term 6-MP. There are data suggesting that patients on long-term maintenance with 6-MP or azathioprine fared better than those who stopped these medications. Those who stopped 6-MP or azathioprine were more likely to experience relapses, more likely to need corticosteroids or undergo surgery[22-24,40].

Methotrexate

Methotrexate is an immunomodulator and anti-inflammatory medication. Methotrexate has been used for many years in the treatment of severe rheumatoid arthritis and psoriasis, and is helpful in treating patients with moderate to severe CD who neither respond to 6-MP and azathioprine nor tolerate these two medications. Methotrexate may also be effective in patients with moderate to severe UC who do not respond to corticosteroids or 6-MP and azathioprine. It can be given orally or by weekly

injections under the skin or into the muscles. It is more reliably absorbed with the injections[35-39]. One major complication of methotrexate is the development of liver cirrhosis when the medication is given over a prolonged period of time (years). The risk of liver damage is higher in patients who also abuse alcohol or have morbid (severe) obesity. Generally, periodic liver biopsies are recommended for a patient who has received a cumulative (total) methotrexate dose of 1.5 g and higher[38-40].

Other side effects of methotrexate include low white blood cell counts and inflammation of the lungs.

Methotrexate should not be used in pregnancy.

Cyclosporine

Cyclosporine (Sandimmune) is a potent immunosuppressant used in preventing organ rejection after transplantation. It has also been used to treat patients with severe UC and CD. Because of the approval of infliximab (Remicade) for treating severe CD, cyclosporine will probably be used primarily in severe UC. Cyclosporine is useful in fulminant UC and severely ill patients who do not respond to systemic corticosteroids. Cyclosporine is available as an oral medication, but the relapse rate with oral cyclopsorine is high. Therefore, cyclosporine seems most useful when administered intravenously in acute situations[33-37].

Side effects of cyclosporine include high blood pressure, renal function impairment, and tingling sensations in the extremities. More serous side effects include anaphylactic shock and seizures.

Traditional Chinese medicine

A total of 10 218 patients with UC reported in Chinese medical literature and the cases diagnosed were analyzed according to the diagnostic criteria of Lennard-Jones from 1981 to 2000. The number of cases increased by 3.08 times over the past 10 years (2 506 patients were diagnosed from 1981 to 1990 while 7 512 patients were diagnosed from 1991 to 2000). Lesion range was described in 7 966 patients, 5 592 (70.2%) were proctosigmoiditis or proctitis, 1 792 (22.5%) left-sided colitis, 582 (7.3%) pancolitis. Among the 8 122 patients, 2 826 (34.8%) had first episode, 4 272 (52.6%) had chronic relapse, 869 (10.7%) were of chronic persistent type, 154 (1.9%) were of acute fulminant type. The course of the illness wwas described in 5 867 patients, 4 427 (75.5%) were less than 5 years, 910 (15.5%) between 5 and 10 years, 530 (9.1%) more than 10 years. Six hundred and sixteen patients (6.1%) had extraintestinal manifestations. The mean age at the diagnosis was 40.7 years (range 6-80 years, and the peak age 30-49 years). The male to female ratio was 1.09. Among the 270 patients diagnosed in our hospital, 36 had histories of smoking, there was no negative association between the severity of UC and smoking (P>0.05), 21 smokers were followed up for one year, 15 of them had given up smoking when the disease was diagnosed, and one year later, 7 patients relapsed, another 6 patients continued smoking, and one year later, 2 patients relapsed. Among the 270 UC patients diagnosed in our hospital, 4 patients (1.5%) from 2 families had a familial history of UC. Treatment was done in 6 859 patients, only 5-ASA and/or corticosteroid only in 1 276 patients (18.6%), Chinese herbs alone in 1 377 patients (20.1%), combined Chinese and Western medicine in 4 056 patients (59.1%), surgery was performed in 87 patients (1.3%), other treatments in 63 patients (0.9%). In China, the number of UC patients increased significantly in the past 10 years. Lesions were commonly located to the left side colon. The course was short with rare extraintestinal manifestations. The age of onset was relatively high. Males and females were nearly equally affected. No negative relation was found between smoking and severity of the disease. Familial relatives were rarely involved. Traditional Chinese medicine (TCM) was widely used in the treatment of UC[33].

Langmead *et al*.[41] reported that herbal remedies for the treatment of IBD included slippery elm, fenugreek, devil's claw, Mexican yam, tormentil and *Wei tong ning*, a traditional Chinese medicine. Reactive oxygen metabolites produced by inflamed colonic mucosa may be pathogenic. Aminosalicylates (5-ASA) are antioxidant and other such agents could be therapeutic. Luminol-enhanced chemiluminescence in a xanthine/xanthine oxidase cell-free system was used to detect superoxide scavenging by herbs and 5-ASA. Fluorimetry was used to define peroxyl radical scavenging by using a phycoerythrin degradation assay. Chemiluminescence was used to detect herbal effects on generation of oxygen radicals by mucosal biopsies from patients with active UC. All materials tested scavenged peroxyl dose-dependently. Oxygen radical release from biopsies was reduced after incubation in all herbs except Mexican yam. All six herbal remedies have antioxidant effects. Fenugreek is not a superoxide scavenger, while Mexican yam does not inhibit radical generation of inflamed biopsies. Slippery elm, fenugreek, devil's claw, tormentil and *Wei tong ning* are novel drugs in IBD.

A total of 118 patients with UC were treated by integration of traditional Chinese and Western medicine[42-44]. Another 86 cases of UC were treated by simple Western drugs as controls. The therapeutic effects on both groups were observed and compared after two therapeutic courses of 40 consecutive days. As a result, 39 cases were cured, 60 cases improved and 19 cases failed, with a total effective rate of 84% in the treatment group. In the control group, 15 cases were cured, 37 cases improved and 34 cases failed, with a total effective rate of 60.5%. Statistically, the difference was very significant (P<0.01). It can be concluded that treatment of UC by the integrated method is superior to that by simple Western drugs[40].

Treatment of chronic UC by traditional Chinese and Western medicine is safe and effective in maintaining remission[41-44].

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